

1. The Examiner's Rejection for Double Patenting

Claims 37-41, 49-51 and 62-64 are provisionally rejected under the judicially created doctrine of double patenting over Claims 37-44, 46-50, 52 and 56-57 of copending application no. 08/333,680. The Applicants are prepared to file a terminal disclaimer in the appropriate application at such time as a patent issues in either application, pursuant to 37 C.F.R. §1.321 (b).

2. The Rejections Under 35 U.S.C. § 102  
Should Be with Withdrawn

Claim 62 drawn to a replication-defective recombinant adenovirus is rejected under 35 U.S.C. §102(e) as anticipated by Gregory et al. U.S. Patent No. 5,670,888 ("Gregory").

Claim 62 is drawn to recombinant adenovirus that requires at minimum complementation of the E1 and E4 early gene regions in the absence of the expression of additional adenoviral gene regions in trans. Briefly, the Examiner contends that Gregory anticipates the recombinant adenoviruses of the present invention which comprise a lethal deletion of E4 and a lethal deletion in E1, E3, E2A or viral structural genes, and further comprising a transgene under the human PGK promoter gene regions. This rejection is in error for the reasons explained below.

The legal test for anticipation under 35 U.S.C. § 102 requires that each and every element of the claimed

invention be disclosed in a prior art reference in a manner sufficient to enable one skilled in the art to reduce the invention to practice, thus placing the public in possession of the invention. W.L. Gore Associates v. Galock, Inc., 721 F.2d 1540, 1554 (Fed. Cir. 1983) cert. denied 469 U.S. 857 (1984); In re Donohue, 766 F.2d 351 (Fed. Cir. 1985).

Anticipation under 35 U.S.C. § 102 requires identity of invention. Scripps Clinic & Research Fdn. v. Genentech Inc., 927 F.2d 1565 (Fed. Cir. 1991). Anticipation under 35 U.S.C. §102 also requires that the prior art reference places the claimed invention in the possession of the public through an enabling disclosure. Charles v. Miller, 906 F.2d 1574, 15 USPQ 2d 133 (Fed. Cir. 1990).

In this instance, the invention as claimed relates to a replication-defective recombinant adenovirus which requires for replication complementation of genes of both the E1 and E4 early gene regions in the absence of expression of additional adenoviral gene regions in trans. Gregory does not anticipate the recombinant adenoviruses and vectors of the present invention which contain at least two lethal deletions in the E1A, E2A or E4 early gene regions and require complementation with E1A and E4 gene regions for rescue in the absence of expression of additional adenovirus genes, or the genomes thereof. The only packaged recombinant adenovirus described in Gregory is one which must retain the essential region of E4, ORF6, so that complementation with E4 is not required to achieve rescue of the adenoviral vector. Gregory

does not teach and enable the production of adenoviruses with deletions of the essential regions of E1 and E4. It simply was not known how to provide the essential functions of both E4 and E1A in a "non-suicidal" packaging cell line.

The essence of the adenoviruses and viral vectors of the present invention is the requirement of complementation of these gene regions without the expression of additional adenoviral gene regions in trans. The deletion of two essential regions in the packaged recombinant adenovirus, e.g., either the E1, E2A or E4 regions, dramatically minimizes or eliminates the pathogenic effects of direct cytotoxicity to the targeted cells and inflammatory responses in the human body. The resulting virus, however, is replication-defective and requires the essential functions in trans in order to replicate.

Prior to the present invention, it was not possible to generate a recombinant adenovirus containing lethal deletions in all of the essential regions of the E1, E2A and E4 gene regions. This is due to the fact that once the DNA encoding the adenoviral genome had been manipulated to contain these deletions, there was no way to provide the toxic gene products encoded by the E1, E2A and E4 gene regions in trans in order to rescue a packaged recombinant adenovirus. This problem was not solved by Gregory, as Gregory does not accomplish nor enable rescue of a recombinant adenovirus carrying a lethal deletion of the E4 early gene region. In fact a close inspection of the working examples of Gregory

reveals that the adenoviral vectors described in Example 15 contain the ORF6 of the E4 gene region which as Gregory points out "was added back to the E1-E4 backbone of the Ad2-ORF6/PGK-CFTR vector because ORF6 function is essential for production of the recombinant virus in 293 cells" (see Gregory Col. 47, lines 58-61).

Gregory does not describe a rescued recombinant adenovirus which carries a lethal deletion in the E4 early gene region, since Gregory does not describe a method of successfully supplying the E4 functions in trans which is necessary to rescue an adenoviral genome containing a lethal deletion or mutation in the E4 early gene region. Rather, Gregory describes a recombinant adenovirus packaged from an adenoviral genome containing a deletion in all of the E4 open reading frames, however, leaving intact the essential E4 open reading frame 6 (ORF6) in order to maintain E4 functions in the virus. However, these deletions of non-essential regions as described in Gregory do not constitute the lethal deletions of E1 and E4 in the replication defective recombinant adenoviruses of the present invention. In fact, the adenoviral vectors as claimed by Gregory require that sufficient E4 sequences are maintained within the viral vectors to promote virus replication.

In summary, Gregory does not describe a recombinant adenovirus, or the rescue of an adenoviral vector, which contains a lethal deletions in the E4 early gene regions, because it was simply not known how to successfully supply the

E4 early gene products in the absence of additional adenoviral gene products in trans without killing the packaging cell line. It is the instant invention that provides recombinant adenoviruses containing these lethal mutations, that are successfully rescued and packaged by complementation with E1, E2, and E4 in trans.

Thus, the recombinant adenoviruses and vectors of the present invention are not anticipated by the cited art and, therefore, the Examiner's rejections under 35 U.S.C. § 102(e) should be withdrawn.

3. The Rejections Under 35 U.S.C. § 112 First Paragraph, Should Be Withdrawn

Claims 42 and 51 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains. As requested by the Examiner, Applicants submit herewith a Deposit Declaration specifying that all restrictions on availability of the deposited materials will be irrevocably removed upon granting of a patent. The submission of this Declaration obviates the Examiner's rejection, therefore the rejections under 35 U.S.C. §112, first paragraph should be withdrawn.

4. The Rejections Under 35 U.S.C. § 112 Second Paragraph, Should Be Withdrawn

Claims 38-41, 49-51, 62 and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing

to particularly point out and distinctly claim the subject matter of the present invention.

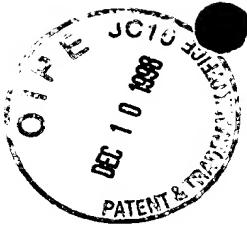
Claims 38, 51 and 62 have been amended as suggested by the Examiner to more distinctly claim the invention, thus obviating the Examiner's rejections of these claims.

The Examiner has rejected Claims 49-50, 62 and 63 as vague and indefinite since the metes and bounds of the term "regions" are undefined since it is unclear what other adenoviral sequences are included. The Examiner's rejection of these claims is based on a misinterpretation of the term "adenoviral gene regions". Adenoviral gene regions is a term of art used by those of ordinary skill to describe specific regions of the adenoviral genome<sup>1</sup>, and it would be clear to one of ordinary skill what is encompassed by the term adenoviral gene region. Thus, Claims 49, 50, 62 and 63 distinctly claim the subject matter of the invention.

Thus, the Claims as amended distinctly and definitely claim the subject matter of the present invention, and the Examiner's rejection under 35 U.S.C. §112, second paragraph should be withdrawn.

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<sup>1</sup> See, e.g. Horowitz, "Adenoviridae and Their Replication" in Fundamental Virology, Second Edition, edited by B.N. Fields, D.M. Knipe et al., Raven Press, Ltd., N.Y. (1991).



CONCLUSION

Applicants respectfully request entry and consideration of the foregoing amendments and remarks.

Applicants believe the claims to be in condition for allowance.

Respectfully submitted,

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Enclosure